REMARKS

Applicant and Applicant's representative wish to thank the Examiner for the courtesies extended during the telephonic interview on September 7, 2010 ("the Interview").

In view of the Non-Final Office Action mailed on July 9, 2010 ("the July 9 Office Action"), in which prosecution of the above-identified patent application was reopened, Applicant files this Amendment and Response pursuant to 37 C.F.R. § 1.111.

Claims 1-31 are currently pending. Claims 1-19, 21, 23-25, 28, 29, and 31 have been withdrawn from consideration. Claims 20, 22, 26, 27, and 30 are rejected. Applicant has amended claims 20, 26, 27, and 30 and has canceled claim 22 in accordance with the Examiner's suggestions during the Interview. Support for the amended claims is provided in the specification. Applicant respectfully submits that the patent application and claims, as amended, are in a condition for allowance. Accordingly, reconsideration and allowance of the claims is respectfully requested.

Substitute Specification

The Examiner has not entered the Substitute Specification filed on 10/05/07 because the Examiner alleges that the Substitute Specification "does not conform to 37 C.F.R. § 1.125(b) and (c) and because it contains new matter." July 9 Office Action, ¶ 3.

In response, Applicant has resubmitted the Substitute Specification filed on 10/05/07, with the following corrections made as required by the Examiner:

(1) Applicant has included the following sentence in the Abstract: "Additionally, the invention provides an NK-92 cell, an NK-92 cell modified by transfection with a vector conferring advantageous properties, which is unable to proliferate and which preserves the effective cytotoxic activity."

(2) Applicant has amended the last sentence of the Abstract to include the following limitation: "that has lost the ability to bind to T-cell receptors."

(3) Applicant has amended the priority claim to delete the phrase "which are all incorporated herein by reference in their entirety," which was made part of the Preliminary Amendment dated October 22, 2003.

(4) Applicant has removed the blank pages accidentally inserted in the Substitute Specification filed on 10/05/07 but not found in the original specification.

For the Examiner's convenience, a marked up copy of the Substitute Specification, showing changes relative to the immediately prior version thereof, is attached hereto as **Appendix A** and a clean copy is attached hereto as **Appendix B**.

Applicant respectfully submits that the cancellation of the alleged new matter in the Substitute Specification overcomes the Examiner's rejection and places the Substitute Specification into conformity with the requirements set forth in 37 C.F.R. § 1.125(b), (c). For these same reasons, Applicant respectfully submits that the Examiner's rejection pursuant to 35 U.S.C. § 132(a) (see July 9 Office Action, ¶ 4) is overcome. Applicant requests that the Examiner enter the Substitute Specification.

Double Patenting

The Examiner has provisionally rejected claims 20, 22, 26, 27, and 30 pursuant to the nonstatutory judicially-created doctrine of obviousness-type double patenting as allegedly being unpatentable over claims 30-35, 46, 48, 50, and 53 of copending Application No. 10/701,359, on the grounds that the claims are allegedly not patentably distinct from each other. See July 9 Office Action, ¶ 6. Applicant will file a terminal disclaimer to overcome the double patenting rejection upon indication of allowable subject matter.

Rejection Pursuant to 35 U.S.C. § 112, first paragraph

The Examiner has rejected claims 20, 22, 26, 27, and 30 pursuant to 35 U.S.C. § 112, first paragraph, because the specification allegedly "does not reasonably provide enablement for the claimed method of treating a 'pathology' where said 'pathology' could encompass any diseases wherein the disease was caused by cells that could not be lysed/recognized by NK-92 cells." July 9 Office Action, ¶ 8.

Applicant has amended the claims to be limited to "a method of treating a cancer...wherein said cancer is recognized and lysed by said NK-92 cell line", in accordance with the claim amendment discussed with the Examiner during the Interview. Applicant respectfully notes that the Examiner indicated that the specification is "enabling for the claimed method wherein the disease treated is cancer and wherein the cancer cells can be lysed/recognized by NK-92." July 9 Office Action, ¶ 8. Applicant respectfully submits that the claim amendments overcome the Examiner's rejection. Withdrawal of the rejection of claims 20, 26, 27, and 30 is respectfully requested. Applicant notes that claim 22 has been canceled.

Rejection Pursuant to 35 U.S.C. § 103(a) Over Gong et al. in view of Santoli et al.

The Examiner has rejected claims 20, 22, 26, 27, and 30 as allegedly being unpatentable over Gong et al. in view of U.S. Patent No. 5,272,082 to Santoli et al. ("Santoli et al."). Claim 20, from which claims 26, 27, and 30 depend, requires "A method of treating a cancer *in vivo* in a mammal comprising the step of administering to the mammal a medium comprising an NK-92 cell line ATCC Deposit No. CRL-2407, wherein said cancer is recognized and lysed by said NK-92 cell line." Applicant respectfully traverses the Examiner's basis for rejecting the claimed method because Gong et al. in view of Santoli et al. does not teach or suggest Applicant's claimed method of treatment, let alone the specific cell line, for at least the reasons explained

below and those previously submitted in the Amendment and Response dated October 5, 2007 (the "Initial Response") and the Request for Continued Examination dated October 15, 2008 (the "RCE")[1], which are each is incorporated as if set forth entirely herein. As set forth in the Initial Response and the RCE, although Santoli et al. disclose that T-ALL cells can be used *in vivo*, that disclosure does not suggest Applicant's claimed method of treating a cancer. Accordingly, Applicant respectfully requests the Examiner reconsider the application in view of the claim rejection, and issue a notice of allowance.

As a preliminary matter, NK-92 cells are structurally and functionally distinct from the T-ALL cells taught by Santoli et al. Declaration of Hans Klingemann, M.D., Ph.D. Pursuant to 37 C.F.R. § 1.132, ¶ 28, filed in conjunction with the Response to Final Office Action dated October 15, 2008 (hereinafter, "Klingemann Decl., ¶ __"). Comparative studies have demonstrated at least the following distinctions:

NK-92 CELLS	**T-ALL CELLS**
Derived from patient with aggressive LGL lymphoma	Derived from patient with T lymphoblastic leukemia
Originate from natural killer cells	Originate from T-cells
Do not require antibody stimulation in culture	Require antibody stimulation in culture
Maintain cyotoxicity and function after irradiation	Lose some cytotoxicity after irradiation
Have higher cytotoxicity than T-ALL cells	Have lower cytotoxicity than NK-92 cells

See Klingemann Decl., ¶¶ 21-33.

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[1] Note that the RCE was resubmitted in its entirety on January 15, 2009, as part of a Response to Notice of

Because NK-92 cells are inherently different, both structurally and functionally, from the T-ALL cells disclosed by Santoli et al., one skilled in the art would therefore assume that conclusions with respect to one of these cell lines cannot be drawn to the other cell line. Klingemann Decl., ¶ 28a. Thus it is improper for the Examiner to impart characteristics of one onto the other as it would not provide a proper basis of rejection.

The Examiner alleges that "[i]t would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have created the claimed invention because Gong et al. teach use of NK-92 cells to lyse tumor cells, while Santoli et al. teach in vivo use of cytotoxic cell lines. One of ordinary skill in the art would have been motivated to do so because Santoli et al. teach that lytic human derived cell lines can be used in vivo to treat disease or in preclinical in vivo studies." July 9 Office Action, ¶ 10 (citing Santoli et al., col. 10). Applicant disagrees.

The Examiner continues to argue that "use of NK cells and LAK cells to treat cancer in vivo was already known in the art. Gong et al. disclose that the NK-92 cell line displays characteristics of NK cells, wherein use of NK cells to treat cancer in vivo was already known in the art." July 9 Office Action, ¶ 10. In fact, these earlier disclosures of NK and LAK cells are irrelevant. The Examiner's overly broad and unsupported conclusion fails to consider that NK cells and LAK cells are quite different from Applicant's NK-92 cells. In fact, Applicant's disclosure actually details the limitations of using NK and LAK cells *ex vivo* and *in vivo*. See Specification, 4:4-23. Applicant specifically notes that "[t]here thus remains a need for a method of treating a pathology related to cancer or a viral infection with a natural killer cell line that maintains viability and therapeutic effectiveness against a variety of tumor classes." Id., 4:24-

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Noncompliant Amendment.

26. Gong et al.'s recognition in the Abstract that the novel NK-92 cell line "displays characteristics of activated NK-cells and could be a valuable tool to study their biology" does not impact the patentability of Applicant's claimed method for two reasons: first, because Gong et al. fail to disclose that NK-92 cells could be used for *in vivo* treatment of cancer; and second, because there was simply no motivation to look to Santoli et al., whose disclosure is limited to T-ALL cells, for such a teaching. The differences between NK-92 cells and T-ALL cells known at the time of filing Applicant's claimed method were so great that it was unlikely that one skilled in the art would have found T-ALL cells to provide any teaching with respect to NK-92 cells. Klingemann Decl., ¶ 28. The necessary nexus between the NK-92 cells taught by Gong et al. and an *in vivo* treatment of cancer that would have led one of skill in the art to look to the teachings of Santoli et al. is missing, as detailed in the Initial Response, the RCE, and below.

The Examiner states that "both the cells described by Santoli et al. and NK-92 are lytic human derived cell lines that can lyse various tumor cells." July 9 Office Action, ¶ 10. This conclusion is inaccurate because Gong et al. do not teach that NK-92 cells are capable of lysing various tumor cells of different origin or type. Klingemann Decl., ¶ 24. Instead, Gong et al. teach that NK-92 cells demonstrated cytotoxicity against two human leukemic cell lines in studies developed to characterize the newly isolated cell line. Further, given the significant phenotypic and functional differences between NK-92 cells and T-ALL cells, there would not have been any reason apparent to one skilled in the art at the time the claimed method was developed to look to Santoli et al.'s teaching of T-ALL cells to arrive at a method of treating a pathology *in vivo* in a mammal by administering NK-92 cells. Klingemann Decl., ¶ 29. Thus, contrary to the Examiner's conclusion, because Gong et al. do not teach that technique it could not be obvious to use it to arrive at, let alone improve, another technique.

The Examiner also states that "there is no teaching in Gong et al. that NK-92 cells are unacceptable for in vivo use." July 9 Office Action, ¶ 10. That notation, however, is irrelevant. What the reference does not teach is irrelevant to an obviousness analysis; the only relevant factor is what the reference does teach. See, e.g., M.P.E.P. § 2143.01, citing KSR Int'l v. Teleflex Inc., 127 S.Ct. 1727, 1740-1741 (2007) (stating that "rejections on obviousness cannot be sustained by mere conclusory statements; instead, there must be some articulated reasoning with some rational underpinning to support the legal conclusion of obviousness"). Here, Gong et al. do not teach or suggest that the NK-92 cells disclosed therein could be used *in vivo* to lyse tumor cells. Klingemann Decl., ¶ 24. In fact, the inventor did not even recognize the importance or utility of the NK-92 cell line in a clinical setting. Klingemann Decl., ¶ 24. Rather, the NK-92 cell line provided a suitable model to study the biology of NK-cells and activated NK-cells. Klingemann Decl., ¶ 22. Gong et al. partially characterized the cytotoxic profile of NK-92 cells. Klingemann Decl., ¶ 23. Any alleged teaching in Santoli et al. with respect to "a need for therapeutic methods for treating cancers using cytotoxic cell lines" is irrelevant because, given the significant phenotypic and functional differences between NK-92 cells and T-ALL cells, there was no reason apparent to one skilled in the art to combine the references or to look to Santoli et al.'s teaching of T-ALL cells to arrive at similar methods of treatment with NK-92 cells. Klingemann Decl., ¶¶ 27-29.

The Examiner concludes that "NK-92 cells could be used in patients that contained tumor cells that were not lysed by TALL cells." July 9 Office Action, ¶ 10. This conclusory statement is inappropriate because citing "rejections on obviousness cannot be sustained by mere conclusory statements; instead, there must be some articulated reasoning with some rational underpinning to support the legal conclusion of obviousness." KSR Int'l v. Teleflex Inc., 127

S.Ct. 1727, 1740-1741 (2007). Here, the Examiner has failed to provide any reasoning to support this conclusion. Santoli et al. is limited to teachings with respect to T-ALL cells. "Simply because one cell line has a specific utility does not mean that other closely related cell lines will have the same utility. Each must be proven independently and the specific conditions necessary for successful results, including treatment, determined." Klingemann Decl., ¶ 27. Moreover, if NK-92 cells could be used in patients that contained tumor cells that were not lysed by TALL cells, then, in fact, Santoli et al. may actually serve as a teaching away from Applicant's claimed method. Regardless, the Examiner has made inappropriate, baseless conclusions and, in so doing, has failed to satisfy his burden of establishing a *prima facie* case of obviousness pursuant to 35 U.S.C. § 103.

The Examiner cites to the M.P.E.P. § 2121, stating that "when the reference relied on expressly anticipates or makes obvious all of the elements of the claimed invention, the reference is presumed to be operable. Once such a reference is found, the burden is on applicant to provide facts rebutting the presumption of operability." July 9 Office Action, ¶ 10. In response, Applicant replies that the combination of references fails to make obvious all of the elements of Applicant's claimed method for at least the reasons set forth above and in the Initial Response and RCE. As such, the burden has not shifted to Applicant to rebut the presumption of operability. Even if the burden has shifted, however, the combination of references is not operable because "[s]imply because one cell line has a specific utility does not mean that other closely related cell lines will have the same utility. Each must be proven independently and the specific conditions necessary for successful results, including treatment, determined." Klingemann Decl., ¶ 27. Any teaching in Santoli et al. with respect to the operability of T-ALL cells is completely inapplicable to NK-92 cells and the method of using NK-92 as an *in vivo*

treatment. Thus, even if the burden has shifted to Applicant to rebut the presumption of operability, Applicant has met such burden.

The Examiner also cites to M.P.E.P. § 2143.02 to support his position that "obviousness requires only a reasonable expectation of success." July 9 Office Action, ¶ 10. The Examiner states that "[r]egarding the Klingemann declaration, Santoli et al. teach there is a need for cytotoxic cell lines which could be used to treat cancer. In view of the high level of skill in the art (Ph.D. or MD, with extensive research training) it would have been obvious to a routineer that other cytotoxic cell lines could be potentially used as per Santoli et al." Id. In fact, it is exactly this requisite high level of skill in the art that allows one to appreciate the complexity and uniqueness of each cell line and imparts on the skilled artisan the ability to recognize that "know-how with respect to one cell line cannot automatically be transferred or applied to another cell line, even where the cells are closely related...." Klingemann Decl., ¶ 27 (emphasis added). Further, the NK-92 cell line of Applicant's claimed method and the T-ALL cells disclosed by Santoli et al. are not even comparable or related, making any teaching in Santoli et al. with respect to T-ALL cells completely inapplicable. Klingemann Decl., ¶¶ 28, 29. Notably, "comparative studies of NK-92 cells and TALL-104 cells further demonstrate that these cell lines are functionally quite different, with NK-92 cells having significantly higher cytotoxic activity than TALL-104 cells." Klingemann Decl., ¶¶ 31, 32; see also Specification, Tables 5, 6, and Figure 9.

The Examiner further notes that "the use of NK cells to treat cancer in vivo was already known in the art whilst Gong et al. disclose that the NK-92 cell line displays characteristics of NK cells." July 9 Office Action, ¶ 10. This is an improper conclusion because NK cells and NK-92 cells are distinct cell lines. In fact, Gong et al.'s recognition in the Abstract that the novel

NK-92 cell line "displays characteristics of activated NK-cells and could be a valuable tool to study their biology" does not impact the patentability of Applicant's claimed method for two reasons: first, because Gong et al. fail to disclose that NK-92 cells could be used for *in vivo* treatment of cancer; and second, because there was simply no motivation to look to Santoli et al., whose disclosure is limited to T-ALL cells, for such a teaching.

The Examiner also states that Tam et al. (Human Gene Ther. 1999) states that "an alternative is to use established cytotoxic NK tumor cell lines, which would give access to large numbers of effector cells. This concept has been proved by Cesano et al. (1997), who showed that an NK-like cell, TALL-104 was effective in treating a variety of malignancies in dogs." July 9 Office Action, ¶ 10. The Examiner continues, "contrary to the comments in the Klingemann declaration, Tam et al. disclose that TALL-104 is an NK-like cell line which is similar enough to NK cells that findings using TALL-104 cells can be extrapolated to NK cell lines." Unfortunately, the Examiner neglects to consider the entirety of the discussion in Tam et al., namely, that "NK-92 cells were shown to have a higher cytolytic activity and to kill a broader spectrum of malignant target cells than the TALL-104 cell line." Tam et al., 1370. This further emphasizes the distinctions between NK-92 and TALL-104 cell lines.

The Examiner also states that "Klingemann et al. (1996) also disclose that NK-92 and TALL-104 cells having similar lytic properties." July 9 Office Action, ¶ 10. This is a misstatement of Klingemann et al. Rather, Klingemann et al. states that "[a] comparative study of the cytotoxic activity of the TALL-104 and the NK-92 cells has suggested, however, that NK-92 cells display a higher level of cytotoxicity than TALL-104 against leukemic and lymphoma targets and also lyse a broader spectrum of leukemic target cells including primary leukemias derived from patients." Klingemann et al., 73 (emphasis added). Furthermore, as stated in the

Klingemann Declaration, "comparative studies of NK-92 cells and TALL-104 cells further demonstrate that these cell lines are functionally quite different, with NK-92 cells having significantly higher cytotoxic activity than TALL-104 cells." Klingemann Decl., ¶ 31. "In fact, data disclosed in the [Specification] demonstrate that NK-92 cells are more cytolytic than TALL-104 cells or YT cells." Klingemann Decl., ¶ 32 (emphasis added), citing Specification, Tables, 5, 6, and Figure 9. For at least these reasons, any teaching in Santoli et al. with respect to TALL cells is inapplicable to, and cannot obviate, Applicant's claimed method of treating a cancer *in vivo* comprising administering an NK-92 cell line.

The Examiner also states that Gong et al. states that "NK-92 cells require IL-2 for continued growth." July 9 Office Action, ¶ 10. Applicant respectfully points out to the Examiner that Applicant's NK-92 cells are used to treat cancer after the cells have been washed and IL-2 fully removed from the medium and then cells are irradiated so that further growth is terminated. As such, any teaching in Gong et al. with respect to IL-2 is inapplicable to, and cannot obviate, Applicant's claimed method of treating a cancer *in vivo* comprising administering an NK-92 cell line.

The Examiner also states that "[r]egarding applicants comments about long-felt need, similar cells and methods were already known in the art (aka TALL-104 as per Santoli et al.)." July 9 Office Action, ¶ 10. In fact, for the reasons set forth above and in the Initial Response and RCE, any teaching in Santoli et al. with respect to TALL cells is inapplicable to, and cannot obviate, Applicant's claimed method of treating a cancer *in vivo* comprising administering an NK-92 cell line. The Examiner has failed to establish "similarity" sufficient to obviate Applicant's claimed method of treating a cancer. Santoli et al.'s "T-ALL cell line is not even comparable or related to the NK-92 cell line" of Applicant's claimed method. Klingemann

Decl., ¶ 28; see also Klingemann Decl., ¶¶ 27, 29, 31, 32. The results demonstrating that the NK-92 cell line is a superior cell line to the TALL-104 cell line were surprising. Klingemann Decl., ¶ 33. Successful results and evidence of discovery further establish the patentability of Applicant's claimed modified NK-92 cells. "[O]bjective evidence such as commercial success, failure of others, long-felt need, and unexpected results must be considered before a conclusion on obviousness is reached." *Minnesota Mining & Manufacturing Co. v. Johnson & Johnson Orthopedics, Inc.*, 976 F.2d 1559, 1573 (Fed. Cir. 1992) (noting the importance of secondary considerations in the obviousness analysis), citing *Hybritech Inc. v. Monoclonal Antibodies, Inc.*, 802, F.2d 1367, 1379-80, 231 USPQ 81, 90 (Fed. Cir. 1986). Recent clinical trial studies demonstrated the "feasibility of large-scale expansion and safety of administering NK-92 cells as allogeneic cellular immunotherapy in advanced cancer patients and serves as a platform for future study of this novel natural killer (NK)-cell based therapy." (Cytotherapy 10(6): 625-632, 2008). The methods used were tailored to NK-92 cells, which are very different from the methods tailored to T-ALL cells. Klingemann Decl., ¶ 35.

The Examiner also states that "[t]he claimed method is an in vivo method of treatment and there is no evidence of record that in vivo treatment with NK-92 cells is superior to in vivo treatment with TALL-104 cells." Regardless, "data disclosed in the [Specification] demonstrate that NK-92 cells are more cytolytic than TALL-104 cells or YT cells." Klingemann Decl., ¶ 32 (emphasis added), citing Specification, Tables, 5, 6, and Figure 9. As such, the utility of NK-92 cells was surprising. It was unexpected that NK-92 cells would yield such high cytolytic activity. Klingemann Decl., ¶ 33. For at least these reasons, any teaching in Santoli et al. with respect to TALL cells is inapplicable to, and cannot obviate, Applicant's claimed method of treating a cancer *in vivo* comprising administering an NK-92 cell line.

The Examiner also states that "the Arai publication supplied with the Klingemann declaration states that their trials were phase I wherein 'Efficacy was not determined in this phase I trial." This is inapplicable to the obviousness issue at hand and, in fact, do support that unexpected results were obtained with NK-92 cells. Further, Applicant respectfully points out that Efficacy is reserved for Phase II and Phase III trials. In Aria et al., the results were quite unexpected with unoptimized exposure of NK-92 and in a population that had progressive disease during the last palliative course of treatment.

The Examiner also states that "it would have required nothing more than routine experimentation to create the claimed invention." July 9 Office Action, ¶ 10. Applicant disagrees. There was nothing at the time of Applicant's invention to suggest Applicant's approach. In fact, as set forth above, it is exactly this requisite high level of skill in the art that allows one to appreciate the complexity and uniqueness of each cell line and imparts on the skilled artisan the ability to recognize that there is much more than "routine experimentation" required to create the claimed method. "Given the significant phenotypic and functional differences between NK-92 cells and T-ALL cells and the cytotoxic superiority of NK-92 cells to TALL-104 cells, there was no reason apparent to one skilled in the art as of the filing date of the '955 Application to look to Santoli et al.'s teaching of ALL cells for treatment of disease for any teaching with respect to the NK-92 cells disclosed in Gong et al." Klingemann Decl., ¶ 34.

For at least these reasons, one skilled in the art of tumor immunology would not have combined Gong et al. with Santoli et al. at the time of Applicant's invention to arrive at the claimed method of treating a cancer *in vivo* in a mammal by administering a medium comprising the NK-92 cell line.

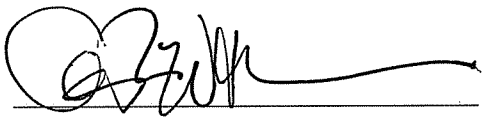
Conclusion

Applicant respectfully submits that the application and claims are in condition for allowance. Accordingly, reconsideration and allowance of all claims are respectfully requested.

Applicant would appreciate the courtesy of a telephone call should the Examiner have any questions or comments with respect to this response or the claim language for purposes of efficiently resolving same.

The Commissioner is hereby authorized to charge Deposit Account No. 03-2026 for any fees associated with this Amendment and Request for Reconsideration.

Respectfully submitted,

By 

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APPENDIX A

Substitute Specification, Marked Up Copy